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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/582,778	08/17/2006	Jean Lafay	06076	5038

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EXAMINER	
HAVLIN, ROBERT H	

ART UNIT	PAPER NUMBER
1626	

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10/15/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/582,778	LAFAY ET AL.	
	Examiner	Art Unit	
	ROBERT HAVLIN	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *15-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 June 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/13/06 and 4/29/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims: Claims 1-31 are currently pending.

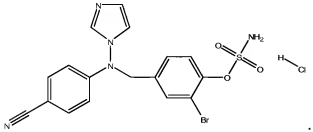
Priority: This application is a 371 of PCT/EP04/14847 (12/15/2004) and claims foreign priority to EUROPEAN PATENT OFFICE (EPO) 03 293 152.9 (12/15/2003) and EUROPEAN PATENT OFFICE (EPO) 04 292 681.6 (11/12/2004).

IDS: The IDS dated 6/13/06 and 4/29/09 were considered.

Election/Restrictions

1. Applicant's election with traverse of a Group I (claims 1-31 where Z is ) in the reply filed on 7/9/09 and 4/29/09 is acknowledged. The traversal is on the ground(s) that unity of invention was applied improperly. This is not found persuasive because the claims do not share a substantial structural feature that is essential to the utility nor is it a contribution over the prior. The lack of unity of invention is further evidenced by the fact that the non-variable common structural feature is known in the prior art as cited in the requirement for restriction and as described in the following rejection.

The requirement is still deemed proper and is therefore made FINAL. Application also elected the following species (example 45 allegedly reading on claims 11-14; interpreted by the examiner to read on claims 1-14):



As detailed in the following rejections, the generic claim encompassing the elected species was not found patentable. Therefore, the provisional election of species is given effect, the examination is restricted to the elected species only, and claims not reading on the elected species are held withdrawn. Accordingly, claims 15-31 are hereby withdrawn.

Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection through amendment, the amended Markush-type claim will be reexamined to the extent necessary to determine patentability of the Markush-type claim. See MPEP 803.02.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant uses definitions for substituents that do not provide points of attachment. For example, the definitions of the "Z" groups show structures, but one of ordinary skill in the art would not know how they are attached to the structure of formula I. Thus, one of ordinary skill in the art could not determine the

metes and bounds of the claims and the claims are indefinite. The examiner recommends providing in the claims the specific points of attachment for the alternatives.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while potentially being enabling for the compounds identified as having inhibitory effect with experimental data, does not reasonably provide enablement for the asserted utility of the entirety of the claim scope. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Particularly relevant to the instant case is the issue as to whether the specification provides embodiments allowing use of the claimed invention without requiring undue experimentation by one of ordinary skill in view of the highly unpredictable nature of inhibiting enzymes.

> "[An inventor] must not be permitted to achieve . . . dominance by claims which are insufficiently supported and hence not in compliance with the first paragraph of 35 U.S.C. 112. That paragraph requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Accordingly, the critical element here how broad the claims are compared to the level of unpredictability in the art.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following:

Nature of Invention. The nature of the invention involves pharmaceutical compounds for inhibiting enzymes.

Scope of the Invention. The scope of the invention are for a genus of compounds of formula I having in excess of millions of species.

State of the Art and Level of Skill in the Art. Although the level of skill in the art is very high, inhibiting enzymes is a very unpredictable art. Kubinyi (3D QSAR in Drug Design: Ligand-Protein Interactions and Molecular Similarity, Vol 2-3, Springer, 1998, 800 pages) teaches that very slight perturbations in the structure of an inhibitor (such as the addition of a methyl group or inversion of a chiral center, see p. 243) can have radical effects on the binding of an inhibitor.

Number of Working Examples and Guidance Provided by Applicant. The applicant provides table 1 showing experimental data for approximately 19 compounds, all of which do not fall into the scope of the claims.

Unpredictability of the Art and Amount of Experimentation. The art of using pharmaceuticals to inhibit enzymes is highly unpredictable as described by Kubinyi. In nearly every case, the skilled artisan could not predict *a priori* whether a given pharmaceutical would inhibit an enzyme. When small variations in structure such as the addition of a methyl group has radical effects on the binding of an inhibitor, without specific guidance or correlations indicating how the structure of species affects its ability to inhibit an enzyme the scope of enablement is constrained to compounds showing substantial similarity to those actually demonstrated to be useful. Furthermore, there would be a huge amount of undue experimentation required in order to synthesize and screen the millions of compounds within the claimed scope.

Considering the above factors, the claims are clearly not enabled for the full scope of the compounds claimed. The examiner recommends either amending the claim scope to only those compounds closely resembling the compounds actually tested and disclosed in the specification or provide additional data and/or structural correlations to guide one of ordinary skill in the art to compounds possessing the asserted utility.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The factual inquiries set forth in *Graham* **v.** *John Deere Co.,* 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

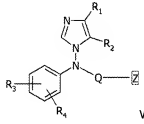
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. Claims 1-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Okada et al. (US 5,674,886) in view of Wermuth (C. Wermuth, Editor, Practice of Medicinal Chemistry, Academic Press (1996), pp. 203–237), Strehlke et al. (US 5,045,558), Bowman et al. (US 4,978,672), and Bowman et al. (US 4,937,250).

The instant claims read on compounds including the species of:

The instant claims are for pharmaceutical compounds that are aromatase inhibitors.

Specifically, the claims read on a species of formula (I):

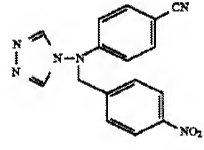


where Q-Z is  ; R1, R2 are H; R3 is CN; R4 is H; R8 is NO2; R9 is H.

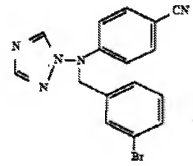
1. Determining the scope and contents of the prior art.

Okada (US 5,674,886) teaches pharmaceutical compounds as aromatase inhibitors

Example 22 on col 24:



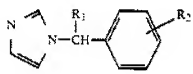
51
EXAMPLE 68



and in col 51:

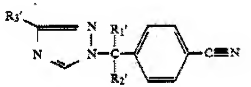
Strehlke (US 5,045,558) teaches aromatase inhibitors of the following formula:

What is claimed is:
1. An imidazole of the formula



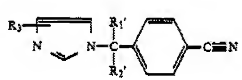
Bowman (US 4,978,672) teaches aromatase inhibitors of the following formula:

34



Bowman (US 4,937,250) teaches aromatase inhibitors of the following formula:

3. A compound according to claim 1 of the formula



(II)

Wermuth teaches the methodologies routinely employed in drug discovery. Wermuth specifically teaches how ring equivalents can be substituted while maintaining pharmaceutical activity in a strategy called isostereism that is well known in the art. Table 13.6 provides specific examples where this strategy was successful. In addition, on page 211 the reference teaches "[t]he substitution of –CH= by –N= . . . in aromatic rings has been one of the most successful applications of classical isostereism."

2. *Ascertaining the differences between the prior art and the claims at issue.* The difference between Okada's example 22 and the instant claims is the 1,2,4-triazole ring versus the imidazole ring. In other words, the –N= or the triazole ring in Okada was replaced with a –CH= group.

3. Resolving the level of ordinary skill in the pertinent art.

One of ordinary skill in the art of pharmaceutical development would be well versed in the teachings of references such as Wurmuth. One of ordinary skill in the art would consider routine and well within their technical grasp the process of altering the chemical groups on drug molecules in an isosteric optimization strategy and screen them for activity on a large scale to improve potency.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The application does not provide a comparison of above cited prior art with the instantly claimed invention. The application does not provide any other evidence of other secondary considerations.

One of ordinary skill in the art would be motivated to optimize the drug identified by Okada and perform the methods of isosterism as taught by Wermuth. Based on the teachings of both Bowman references and Stehlke, one of ordinary skill in the art would be further motivated to alter the triazole ring with the imidazole ring because the prior art references have a substantial structural similarity and are used to solve the same problem as the instant invention. Therefore, one of ordinary skill in the art would have a reasonable expectation of success in performing the modification.

In Eisai Co. Ltd. v. Dr. Reddy's Laboratories Ltd., 87 USPQ2d 1452, 1454 (Fed. Cir. 2008), the Federal Circuit clarified the proof of obviousness in structural similarity situations such as this:

> Where, as here, the patent at issue claims a chemical compound, the analysis of the third Graham factor (the differences between the claimed invention and the

prior art) often turns on the structural similarities and differences between the claimed compound and the prior art compounds. See Eli Lilly & Co. v. Zenith Goldline Pharms., Inc., 471 F.3d 1369, 1377 [81 USPQ2d 1324] (Fed. Cir. 2006) (noting that, for a chemical compound, a prima facie case of obviousness requires "structural similarity between claimed and prior art subject matter … where the prior art gives reason or motivation to make the claimed compositions" (quoting In re Dillon, 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc))). Obviousness based on structural similarity thus can be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (i.e. a lead compound) in a particular way to achieve the claimed compound. See Takeda Chem. Indus. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1356 [83 USPQ2d 1169] (Fed. Cir. 2007). In keeping with the flexible nature of the obviousness inquiry, KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1739 [82 USPQ2d 1385] (2007), the requisite motivation can come from any number of sources and need not necessarily be explicit in the art. See Aventis Pharma Deutschland GmbH v. Lupin, Ltd., 499 F.3d 1293, 1301 [84 USPQ2d 1198] (Fed. Cir. 2007). Rather "it is sufficient to show that the claimed and prior art compounds possess a 'sufficiently close relationship … to create an expectation,' in light of the totality of the prior art, that the new compound will have 'similar properties' to the old." Id. (quoting Dillon, 919 F.2d at 692).

As in Elsai, the prior art compound shows a very close structural relationship to the claimed compound and one of ordinary skill in the art would conclude the modification to imidiazole would have similar properties based on the knowledge and experience of those of ordinary skill in the art as well as the specific teachings in the teachings of the prior art as a whole.

Therefore, **the claims are rejected**.

Double Patenting

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

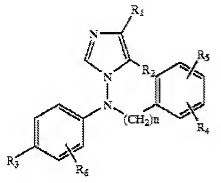
A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 1-14 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-24 of U.S. Patent No. 6,737,433. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are for a genus of compounds that substantially overlaps with the claims of the '433 patent as shown below:

What is claimed is:

1. A derivative of formula (I):



The only apparent difference between the two is the specific list of substituents defined for the variables. One of ordinary skill in the art would find the differences between the two to be obvious variations because both are for the same purpose and the species identified would lead one of ordinary skill in the art to the same compounds.

Conclusion

The claims are not in condition for allowance.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Havlin whose telephone number is (571) 272-9066. The examiner can normally be reached on Mon. - Fri., 7:30am-5pm EST.

If attempts to reach the examiner by telephone are unsuccessful the examiner's supervisor, Joe McKane can be reached at (571) 272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Robert Havlin/
Examiner, Art Unit 1626